**Table S1.** List of the AD prodromal signs and symptoms assessed in the present study.

|  |
| --- |
| **AD prodromal signs and symptoms** |
| * Delusion (ICD9CM: 297.1 including “delusion” in GP’s comments)
 |
| * Psychotic transitory disorders (ICD9CM: 293\*)
 |
| * Hallucinations (ICD9CM: 368.16; 780.1)
 |
| * Agitation (ICD9CM: 307.9 including “agitation” in GP’s comments)
 |
| * Anxiety (ICD9CM: 300\*)
 |
| * Euphoria (ICD9CM: 296.9\* including “euphoria” in GP’s comments)
 |
| * Apathy (ICD9CM: 799.2 including “apathy” in GP’s comments)
 |
| * Disinhibition (ICD9CM: 299.1\*)
 |
| * Irritability (ICD9CM: 312\* including “irritability” in GP’s comments)
 |
| * Aberrant motor behavior (ICD9CM: 307.2\*; 315.4)
 |
| * Night-time disturbances (ICD9CM: 307.41, 307.42, 780.52)
 |
| * Appetite disturbances (ICD9CM: 307.1, 307.50, 307.51)
 |
| * Memory deficit (ICD9CM: 294.0, excluding GP’s comments reporting “Alzheimer disease” or “dementia”; 310.1)
 |
| * Apraxia (ICD9CM: 784.69)
 |
| * Aphasia (ICD9CM: 784.3)
 |

**Table S2.** List of other covariates assessed in the present study.

|  |
| --- |
| **COMORBIDITY**  |
| * Depression (ICD9CM: 296.2, 296.3, 311\*, ever before the period preceding or on the index date)
 |
| * Alcohol abuse and/or alcohol-related diseases (ICD9CM: 303\*, 305.0, 357.5, 425.5, 535.3, 571.0-3, 790.3, V11.3, ever before the period preceding or on the entry date)
 |
| * Diabetes (ICD9CM: 250\*, ever before the period preceding or on the entry date)
 |
| * Ischemic cardiomyopathy (ICD9CM: 410\*-414\*, ever before the period preceding or on the entry date)
 |
| * Stroke (ICD9CM: 430-2\*, 433.01, 433.11, 434.01, 434.11, 436\*, ever before the period preceding or on the index date)
 |
| * Atrial fibrillation (ICD9CM: 427.31, ever before the period preceding or on the entry date)
 |
| * Dyslipidemia (ICD9CM: 272\*; ever before the period preceding or on the entry date, or total cholesterol >200 mg/dL or LDL cholesterol >100 mg/dL or HDL cholesterol <40 mg/dL (for males) or HDL cholesterol <46 mg/dL (for females) or triglycerides >150 mg/dL, as last measurement being registered in the year preceding or on the entry date)
 |
| * Hypertension (ICD9CM: 401\*-405\*, ever before the period preceding or on the entry date, or systolic blood pressure >=140 mmHg or diastolic blood pressure >=90 mmHg, as last measurement being registered in the year preceding or on the entry date)
 |
| * Kidney disease (ICD9CM: 580\*-589\*, 250.4\*, 403\*, 404\*, 274.10, 440.1, 442.1, 453.3, 593\*, 753.0, 753.3, 866\*, including dialysis (ICD9CM: V45.1, V56.0, V56.8) and/or renal transplantation (ICD9CM: V42.0, 996.81) or free text “dialysis” or “renal transplant” (including the presence in a waiting list for renal transplantation), ever before the period preceding or on the entry date), or any GRF value < 60 mL/min/1.73 m2 (last measurement being registered in the year preceding or on the entry date)
 |
| * Charlson Comorbidity Index (CCI) excluding the aforementioned diagnoses (each diagnosis will be captured ever before the period preceding or on the entry date)12
 |
| **PHARMACOTHERAPY** (in the year preceding or on the entry date) |
| * Antihypertensive medications (ATC: C02\*, C03\*, C07\*, C08\*, C09\*)
 |
| * Statins (ATC: C10A\*)
 |
| * NSAIDs (ATC: M01A\*)
 |
| * Low-dose aspirin (ATC: B01AC06)
 |

**Table S3.** Predictors of “certain” Alzheimer Dementia in the 10-year period medical history.

| **Characteristics** | **Cases****n (%)** | **Controls****n (%)** | **Univariate analysis** | **Multivariate analysis** |
| --- | --- | --- | --- | --- |
| **OR (CI 95%)** | **P** | **OR (CI 95%)** | **P** |
| ***Smoking habits (No)*** |  |  |  |  |  |  |
| Yes | 561 (46.87) | 5798 (48.44) | 0.98 (0.76-1.25) | 0.87 | 1.06 (0.81-1.38) | 0.69 |
| Ex | 244 (20.38) | 2112 (17.64) | 1.23 (1.03-1.46) | 0.02 | 1.24 (1.03-1.5) | 0.03 |
| ***BMI (Underweight)*** |  |  |  |  |  |  |
| Normal | 343 (28.65) | 2508 (20.95) | 1.9 (0.95-3.77) | 0.07 | 1.67 (0.8-3.48) | 0.17 |
| Overweight | 327 (27.32) | 3555 (29.7) | 1.27 (0.64-2.53) | 0.49 | 1.14 (0.55-2.39) | 0.72 |
| Obese | 154 (12.87) | 2066 (17.26) | 1.03 (0.51-2.06) | 0.94 | 0.95 (0.45-2.01) | 0.9 |
| ***Psychotic transitory disorders***  | 13 (1.09) | 63 (0.53) | 2.08 (1.14-3.79) | 0.02 | 1.32 (0.65-2.69) | 0.44 |
| ***Hallucination***  | 7 (0.58) | 31 (0.26) | 2.26 (0.99-5.13) | 0.05 | 1.81 (0.71-4.61) | 0.21 |
| ***Agitation***  | 13 (1.09) | 51 (0.43) | 2.57 (1.39-4.75) | <0.001 | 1.93 (0.97-3.83) | 0.06 |
| ***Anxiety***  | 339 (28.32) | 2272 (18.98) | 1.72 (1.5-1.97) | <0.001 | 1.62 (1.4-1.89) | <0.001 |
| ***Aberrant motor behavior***  | 2 (0.17) | 5 (0.04) | 4 (0.78-20.62) | 0.10 | 3.35 (0.56-20.2) | 0.19 |
| ***Night-time disturbances*** | 112 (9.36) | 1187 (9.92) | 0.94 (0.76-1.15) | 0.53 | 0.77 (0.61-0.97) | 0.03 |
| ***Memory deficits*** | 506 (42.27) | 869 (7.26) | 9.68 (8.41-11.14) | <0.001 | 8.31 (7.18-9.63) | <0.001 |
| ***Depression***  | 254 (21.22) | 1247 (10.42) | 2.35 (2.02-2.74) | <0.001 | 2.03 (1.71-2.41) | <0.001 |
| ***Alcohol abuse***  | 5 (0.42) | 52 (0.43) | 0.96 (0.38-2.42) | 0.93 | 0.86 (0.3-2.43) | 0.78 |
| ***Diabetes*** | 130 (10.86) | 1072 (8.96) | 1.24 (1.02-1.51) | 0.03 | 1.64 (1.27-2.11) | <0.001 |
| ***Ischemic cardiomyopathy*** | 44 (3.68) | 621 (5.19) | 0.69 (0.51-0.95) | 0.02 | 0.77 (0.54-1.09) | 0.14 |
| ***Stroke*** | 28 (2.34) | 299 (2.5) | 0.93 (0.63-1.38) | 0.74 | 0.77 (0.5-1.2) | 0.25 |
| ***Atrial fibrillation***  | 4 (0.33) | 67 (0.56) | 0.6 (0.22-1.64) | 0.32 | 0.6 (0.21-1.7) | 0.34 |
| ***Dyslipidemia*** | 419 (35) | 3964 (33.12) | 1.09 (0.96-1.25) | 0.17 | 0.97 (0.83-1.13) | 0.71 |
| ***Hypertension***  | 576 (48.12) | 5872 (49.06) | 0.96 (0.84-1.09) | 0.51 | 1.05 (0.89-1.25) | 0.53 |
| ***Kidney disease***  | 58 (4.85) | 620 (5.18) | 0.93 (0.7-1.23) | 0.61 | 1.37 (0.94-1.98) | 0.1 |
| ***Charlson Comorbidity Index (ref: 0)*** |  |  |  |  |  |  |
| 1 | 222 (18.55) | 2203 (18.4) | 0.98 (0.83-1.15) | 0.78 | 0.81 (0.67-0.99) | 0.04 |
| 2 | 111 (9.27) | 1285 (10.74) | 0.84 (0.68-1.03) | 0.10 | 0.73 (0.56-0.94) | 0.01 |
| >2 | 61 (5.1) | 659 (5.51) | 0.89 (0.68-1.18) | 0.43 | 0.64 (0.44-0.92) | 0.02 |
| ***Antihypertensive medications*** | 439 (36.68) | 4640 (38.76) | 0.9 (0.79-1.03) | 0.12 | 0.86 (0.72-1.03) | 0.11 |
| ***Statins***  | 129 (10.78) | 1227 (10.25) | 1.06 (0.87-1.29) | 0.56 | 0.97 (0.77-1.23) | 0.82 |
| ***NSAIDs*** | 439 (36.68) | 4119 (34.41) | 1.12 (0.98-1.28) | 0.10 | 1.12 (0.97-1.3) | 0.12 |
| ***Low-dose aspirin***  | 97 (8.1) | 923 (7.71) | 1.06 (0.85-1.32) | 0.62 | 1.12 (0.86-1.45) | 0.39 |
|  |  |  |  |  |  |  |

**Missing values: smoking: 3490; BMI: 4081**